

Drug deprescription—withdrawal risk, prevention, and treatment

Madison K. Bangert, MD, and Gabriel M. Aisenberg, MD 

Department of Internal Medicine, McGovern Medical School, UT Health, Houston, Texas

ABSTRACT

In most cases, a sudden interruption of most medications has no major consequences. There are well-recognized therapies that, when withheld, can either lead to the reappearance of the symptoms they were controlling or to signs or symptoms of withdrawal. In this article, we present a table including medications that when interrupted can produce withdrawal syndromes, the signs and symptoms of the withdrawal syndrome, the time to onset and resolution of the syndrome, information regarding alternative delivery options for the drug/s when the oral route is not possible, as well as prevention and therapy.

KEYWORDS Deprescriptions; patient safety; withdrawal

Generally there are no major consequences following sudden interruption of a medication. However, there are well-recognized therapies that, when withheld, can either lead to the reappearance of the symptoms they were controlling or to signs or symptoms of withdrawal. The interruptions may result from inappropriately reconciling the patient's medication list in every encounter, from considering certain medications redundant or unneeded in the inpatient setting without understanding the consequences of stopping them, or from the inability to use the oral route in the case of oral treatments. When there is uncertainty about deprescribing, pharmacists are integral components in the successful discontinuation of inappropriate medications, especially in elderly patients.¹ They can offer valuable information to both physicians and patients.

Symptoms of withdrawal should be distinguished from reappearance of disease symptoms that may reemerge in absence of the treatment. True withdrawal appears when the drug dose reduction is sudden rather than gradual, symptoms are more severe than what they were at baseline, or they appear in newborn infants whose mothers have been taking the drug.²

Table 1 summarizes medications that when interrupted can produce withdrawal syndromes. The table describes the signs and symptoms of the withdrawal syndrome, the time to onset and resolution of the syndrome, information regarding alternative delivery options when the oral route is not possible, and prevention and therapy.

ORCID

Gabriel M. Aisenberg  <http://orcid.org/0000-0003-0826-1427>

Corresponding author: Gabriel Aisenberg, MD, Department of Internal Medicine, McGovern Medical School, UT Health, 6431 Fannin Street, MSB 1.122, Houston, TX 77030 (e-mail: Gabriel.M.Aisenberg@uth.tmc.edu)

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Table 1. Withdrawal syndromes associated with commonly prescribed medications

Drug	Withdrawal effects	Onset/resolution	Alternative delivery options	Prevention/intervention
Opioids ^{3–13}	<ul style="list-style-type: none"> Anxiety, irritability, agitation Diaphoresis, shaking, chills Lacrimation, rhinorrhea Anorexia, nausea, vomiting Cramping Mydriasis Tachycardia, hypertension Increased pain Drug craving 	<ul style="list-style-type: none"> 6–12 hours following short-acting opioid cessation 24–48 hours following long-acting opioid cessation Acute withdrawal may last days to weeks Dependent on the half-life of the drug used 	Intravenous transdermal	<ul style="list-style-type: none"> Long-acting opioid taper by 10% weekly or monthly Methadone maintenance and/or detoxification taper Buprenorphine maintenance and/or detoxification taper Adjuvant therapies to mitigate withdrawal effects: clonidine, gabapentin, topiramate, venlafaxine, buspirone, quetiapine, benzodiazepines (controversial) Restart benzodiazepines to stop acute withdrawal Initiate taper: either weekly dosage reductions of 50% or reduction of daily doses by 10% to 25% every 1 to 2 weeks Individualize the taper on patient tolerance of reduction 4–8 weeks is generally sufficient to complete a safe discontinuation Outpatient reduction is usually acceptable; consider inpatient discontinuation when very high doses are needed
Benzodiazepines ^{14–17}	<ul style="list-style-type: none"> Risk is higher for short-acting benzodiazepines Somatic effects: fatigue, weakness, muscular tension, spasm, pain, sweating, shivering, tremor, tachycardia, hypertension, loss of appetite, seizures Psychological effects: anxiety, agitation, restlessness, depression, emotional lability, difficulties concentrating, delirium, paranoia, hallucinations, derealization, insomnia Sensory effects: hyperacusis, photophobia, dysesthesia, tinnitus, blurred vision 	<ul style="list-style-type: none"> 2–3 days following short-acting benzodiazepine cessation 5–10 days following long-acting benzodiazepine cessation Onset may vary depending on duration and dosages utilized Withdrawal may last 10–14 days 	Intravenous	<ul style="list-style-type: none"> Planned discontinuation: taper 5–10 mg per week as tolerated Acute withdrawal: restart baclofen Supportive care Adjuvant therapies: antipyretics, benzodiazepines, anticonvulsants, dantrolene, antispasmodics, antipsychotics Labetalol (IV) to mitigate withdrawal effects in the short term
Barbiturates ^{2,18, 19}	<ul style="list-style-type: none"> Physical/autonomic effects: weakness, sweating, nausea, vomiting, malaise, headache, dry mouth, fever Psychological effects: insomnia, apprehension, anxiety, irritability, depression, visual hallucinations, delirium Neurological effects: tremor, myoclonus, spasms, seizures Severe withdrawal: repetitive grand mal seizures and delirium, death Psychosis, visual and auditory hallucinations Mood disturbances, agitation Insomnia Confusion, delirium Tachycardia, diaphoresis Spasms leading to rhabdomyolysis Seizures/status epilepticus Intrathecal baclofen withdrawal—can be fatal Tachycardia Agitation/restlessness/irritability Insomnia 	<ul style="list-style-type: none"> Within 24 hours depending on dosage and length of use 24–115 hours generally Neurological effects start within 24–72 hours Hallucinations and delirium arise around 72 hours Fever onset generally at 36–72 hours, lasting 3–4 days 	Intravenous (in status epilepticus)	<ul style="list-style-type: none"> Planned discontinuation: taper 5–10 mg per week as tolerated Acute withdrawal: restart baclofen Supportive care Adjuvant therapies: antipyretics, benzodiazepines, anticonvulsants, dantrolene, antispasmodics, antipsychotics Labetalol (IV) to mitigate withdrawal effects in the short term
Baclofen ^{20–23}		<ul style="list-style-type: none"> 12–24 hours after last dose May take days to develop improvement shortly following reinitiation of baclofen 	Nasogastric tube delivery of a liquid formulation or crushed tablets (in absence of ileus)	
Clonidine ^{2,24–27}		<ul style="list-style-type: none"> May develop within 24 hours after discontinuation 	Transdermal	

Tremors	• Rebound hypertension, sometimes with hypertensive emergency—encephalopathy, retinal and intracranial hemorrhage, acute renal failure, flash pulmonary edema, myocardial infarction	On average, 18–36 hours after last dose	• Clonidine taper: no clear guidelines, gradual (may require a protracted course)
Beta-blockers ^{28–34}	Tachycardia: sinus tachycardia, supra or ventricular tachycardia Nervousness, anxiety, agitation Headache Sweatiness Tremor Nausea	Minor side effects may develop within 24 hours Generally, develops within 3 days Some are delayed to days 14–21	• Phenothiazine + propranolol • Atenolol + prazosin • Benzodiazepines to reduce symptoms In acute withdrawal, reinitiate beta-blockers Taper regimen: reduce daily dose by 50% per week until at lowest dose Maintain lowest dose for 1 week prior to discontinuation
Corticosteroids ^{2,35–38}	Severe complications: angina, myocardial infarction, sudden death Severe fatigue, malaise Hypotension Tachycardia Myalgia, arthralgia Dizziness Mood swings, depression Loss of appetite, nausea, vomiting Diarrhea	Shortly after prolonged steroid use (variable definition, but no less than 4–6 weeks) Hypothalamic-pituitary-adrenal suppression may last weeks to months to a year	• Intravenous (most beta-blockers have short half-lives when administered intravenously; infusions are sometimes necessary)
Psychostimulants ^{2,39–41}	Severe withdrawal: fever, shock, and death Drug seeking “Crash” Lethargy Irritability, aggressiveness, anxiety Difficulties concentrating Anhedonia, depression Suicidal ideation Insomnia or hypersomnia Anxiety Restlessness Irritability Tachycardia Catatonia Seizure Diaphoresis, tachycardia, hypertension Auditory hallucinations, self-mutilation, suicidality Delirium, confusion Psychiatric effects: anxiety, panic attacks, depression, suicidal ideation, agitation, irritability, confusion Autonomic/GI effects: fatigue, nausea, vomiting, orthostatic hypotension, diaphoresis, flushing Sensory effects: diffuse pain, restless legs	Start within 24 hours of the last dose More severe shortly after discontinuation Symptoms generally last ~2 weeks but may persist 3–4 weeks Usually self-limited 24–72 hours after abrupt complete cessation Resolves 24–48 hours after reinstitution of drug	• Self-limiting • Tapering not effective • Antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors), electroconvulsive therapy, dopamine agonists, and anxiolytics helpful for symptom control • Reinitiate gabapentin during acute withdrawal • No clear tapering regimen • Possible regimen: taper doses by 10%–15% weekly
Pregabalin ^{42–44}		None	• Taper the drug for at least a week
Dopamine agonists ^{48–50}		None. There is an intranasal form of levodopa, but no studies supporting beneficial use in dopamine-agonist withdrawal syndrome.	• Tapers are still generally recommended in attempt for prevention, but are not always beneficial • The only known treatment is to restart the dopamine agonist at the last known dose prior to the onset of withdrawal symptoms

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Table 1. Continued

Drug	Withdrawal effects	Onset/resolution	Alternative delivery options	Prevention/intervention
Antidepressants ^{51–55}	<p>Flu-like symptoms: headache, body aches, lethargy, fatigue</p> <p>Sleep disturbance: insomnia, nightmares, vivid dreams “electric shocks”</p> <p>Sensory disturbance: tingling, paresthesia, burning, Psychologic disturbance: labile affect, anxiety, restlessness, mania, cognitive impairment</p> <p>GI disturbance: nausea, loose stools, dry mouth</p> <p>Equilibrium disturbance: ataxia, vertigo, lightheadedness, dizziness</p>	<ul style="list-style-type: none"> • 2–4 days; may start as early as hours after first missed dose • May persist 1–2 weeks if not restarted on antidepressant or tapered • 4–9 months of effective therapy should be completed before elective discontinuation • Less common for fluoxetine due to its long half-life 	<p>None. In Europe, tianeptine (a tricyclic intravenous antidepressant) is available, but not tested for withdrawal</p> <ul style="list-style-type: none"> • • • • • • • 	<p>Tapers vary based on class and specific drug</p> <ul style="list-style-type: none"> • Based on expert opinion • Formulations vary between brand and generic drugs and should be taken into consideration • Fluoxetine is a known exception and generally does not require taper

GI indicates gastrointestinal.

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